REMARKS

Claim Amendment

Claim 33 is amended to recite that a normalization marker characteristic for the presence of epithelial ectocervical or endocervical cells. Support for the amendment can be found at Claim 38 as filed. Consequently, Claim 38 is canceled.

Claim 33 is further amended to recite determining the adequacy of the sample based on the levels of the normalization markers. Support for the amendment can be found at page 47, lines 3-17.

Claim 33 is also amended to delete "their precursor stage" and insert cervical intraepithelial neoplasia. Support for the amendment can be found, for example, at page 9, line 20.

Claim 35 is amended to correct the typographic error of CK13. Claim 35 is further amended to insert p120. Support for the amendments can be found, for example, at Claim 40 as filed.

The other amendments are to amend the claim dependency or to correct the antecedent basis.

No new matter is introduced in any of the above amendments.

Election/Restrictions

The Examiner states that Applicants' election of $p16^{INK4a}$ (Claim 34), EpCam (claim 35), and EpCam (claim 39) with traverse is acknowledged. The Examiner states that Applicant's traversal is unpersuasive because (a) Claim 33 does not constitute a proper linking claim as the proteins listed in claim 34 constitute an improper Markush group, (b) The proteins listed in claims 34 and 35 are separate and distinct.

In response, Applicants have amended Claims 33-35. Claim 34 is amended to recite only $P16^{INK4a}$ and p14ARF, which are closely related because $p16^{INK4a}$ and p14ARF are encoded by the same INK4a/ARF gene locus, and p14 is an alternative reading frame of the p16 gene. $P16^{INK4a}$ and p14ARF share the same utility as a relevant marker. Claim 35 is amended to recite only those normalization markers that are characteristic for the presence of endocercical or

ectocervical cells. Therefore, **Claim 33 is a proper linking claim in view of the claim amendments.**

Although the proteins listed in Claims 34 and 35 are separate and distinct species, the restriction requirement is subject to the non-allowance of the linking claim. Upon the indication of allowability of the linking claim, the restriction requirement as to the linked inventions should be withdrawn and any claim depending from or otherwise requiring all the limitations of the allowable linking claim(s) should be rejoined and fully examined for patentability in accordance with 37 CFR 1.104

Oath/Declaration

The Examiner objects to the Oath/Declaration since an inventor, Mattias Herkert, did not place the date next to his signature.

The Examiner is incorrect because Applicants submitted two Page 3's of the Declaration. One Page 3 contains both Dr. Herkert's signature and date. Therefore, the objection should be withdrawn.

35 USC § 112, second paragraph rejections

Claims 33-40 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. The rejection is traversed in parts and overcome in parts in view of the claim amendments.

a. The Examiner states that Claim 33 is vague and indefinite for the recitation of "cervical cancer and their respective precursor stages." It is unclear what stages are included and what stages are regarded as precursor.

Applicants have amended Claim 33 to delete "their respective precursor stages," thus the rejection is overcome.

b. The Examiner states that Claim 33 recites the limitation "the sample solution" in line 9, but there is insufficient antecedent basis for this limitation in the claim.

Applicants respectfully disagree as line 3 of Claim 33 recites a sample solution, which provides an antecedent basis.

c. The Examiner states that Claim 33 is vague and indefinite because the preamble of claim 33 states "a method for diagnosing cervical dysplasia, cervical cancer" in claim 33, but the method steps read on diagnosing only cervical dysplasia in line 10.

Applicants have amended Claim 33 to overcome this rejection.

35 USC § 112, first paragraph rejection

Claims 33-39 are rejected under 35 U.S.C. § 112, first paragraph, because the specification does not allegedly provide enablement for a method of diagnosing cervical dysplasia by normalizing the level of the relevant marker, p16INK4a, to the normalization marker, EpCam. The rejection is traversed in parts and overcome in parts in view of the claim amendments of Claim 33.

(a). The use of a normalization marker in the context of this invention is merely qualitative, and not quantitative.

The normalization in the present invention avoids false negative results due to inadequate sampling, for example, total amount of patient material not sufficient to perform analysis, or the patient material not taken at the correct anatomical location (see specification at page 47, lines 3-6). The presence of endocervical cells provides the information that the swab or brush has had contact with the columnar epithelium of the endocervix and thus hints to a contact of the swab or brush with the transformation zone, where cervical dysplasia usually originates. In particular, the detection of a certain amount of ectocervical cells (gamma-catenin) together with a certain amount of endocervical cells (Ep-Cam) provides with a high probability the information that the patient material was taken at the correct anatomical location (see specification at page 47, lines 20-26).

To clarify the meaning of the claim that the normalization marker is used for a qualitative purpose, **Applicants have amended Claim 33 to recite that determining the adequacy of the sample based on the levels of the normalization markers detected within the sample solution,** and diagnosing cervical dysplasia based on the levels of the relevant markers and the normalization markers.

(b). Litvinov does not teach using Ep-Cam to indicate the presence of endocervical cells and the adequacy of the sampling.

The Examiner states that Litvinov teaches that Ep-Cam has variable expression in cervical squamous epithelial cells. The Examiner then concludes that the use of Ep-Cam, which has expression levels varied during cancer progression, and which may be a factor contributing to the disturbances in normal differentiation processes in cervical cancer lesions, as a normalization marker is unpredictable.

As discussed above, Ep-Cam is used qualitatively as a normalization marker. The absence of Ep-Cam in a sample indicates that the sample is inadequate for diagnosing a cervical disease. Whereas any detectable signal of Ep-Cam above a certain threshold level indicates that the sample is adequate for testing. The Examiner's argument that Ep-Cam has variable expression in tumor cells is not relevant for the present invention because this is not how Applicants use Ep-Cam as a normalization marker. **Litvinov does not teach using Ep-Cam to indicate the presence of endocervical cells and the adequacy of the sampling.** In the present invention, once a sample is determined to contain EP-Cam at a detectable level, this indicates that there are sufficient numbers of cells present in the sample to allow for a reasonable analysis pertaining to the disease marker.

(c). It is routine experimentation to determine a threshold value of Ep-Cam based on the teaching of the specification.

The Examiner states in Example 5, the specification describes that below a certain threshold (corresponding to 2000 columnar endocervical cells), the sample does not contain an adequate amount of endocervical cells. However, the Examiner states that there is no guidance provided as the possible OD range for a threshold value. Applicants do not agree with the Examiner.

Applicants have provided an OD value of 0.9 as an example for the threshold value of gamma-Catenin, and demonstrated how to diagnose dysplasia based on the levels of $p16^{INK4a}$ and gamma-Catenin. The specification particularly describes that the threshold value applied in this

example are adjusted to the particular reaction conditions. The value for the cells as well for OD may vary depending on the reaction conditions. Thus, the values herein are intended to exemplify the conditions and not to limit the scope of the invention. Those of skill in the art know how an appropriate threshold value for a particular test format may be established. (Page 47, lines 15-20) Based on the example of gamma-Catenin and the guidance of Example 5 regarding Ep-Cam, it is merely routine experimentation for a skilled person to determine a threshold value of Ep-Cam, which indicates the adequacy of endocervical cells, in a test ELISA format.

For the reasons stated above, the 35 USC § 112, first paragraph rejection of Claims 33-39 should be withdrawn.

35 USC § 102(b) rejection

Claims 33, 34, and 36-38 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Von Knebel Doeberitz et al. (U.S. Patent 6,709,832) as evidenced by the National Library of Medicine's MeSH database and Ranki et al. (Journal of Clinical Microbiology 28(9): 2076-2081, 1990). Claim 38 is canceled. The rejection of the remaining claims is traversed because the '832 patent does not teach detecting the level of at least one normalization marker characteristic for the presence of endocervical cells; and determining the adequacy of the sample based on the levels of the normalization markers detected within the sample solution.

The most important aspect for the present invention is that normalization with respect to endocervical cells is made for characterization of the adequacy of the sample, thus avoiding a false negative diagnosis. The most prevalent type of carcinoma of the cervix, namely the Squamous Carcinoma of the Cervix Uteri, arises from the squamous epithelium of the ectocervix, and does not at all contain endocervical cells. Therefore, by detecting Ep-Cam in a sample, it is verified that the sample comprises sufficient endocervical cells. Only in cases that sufficient endocervical cells are present, negative results of p16 may be interpreted as a negative diagnosis. If p16 is negative and Ep-Cam is negative, then the sample is inadequate, as there is a high probability that the sampling device did not reach the endocervical epithelium (see page 47, lines 12 to 26). If p16 is positive in the sample, then the sampling was adequately taken because p16 can only originate from carcinoma cells.

The Examiner states that in the '832 Patent, comparing p16 expression in cervical cancer cells with p16 expression in normal cells constitutes a normalization control. The normalization control in the '832 Patent is different from that of the instant Claim 33. **The '832 Patent compares the levels of the same relevant marker (p16) in two samples**, i.e., a test sample and a normal sample. On the contrary, **Claim 33 determines the levels of two markers, one relevant marker (p16) and one normalization marker (Ep-Cam), within the same human cervical body sample.**

Therefore, the 102(b) rejection of Claims 33, 34, 36, and 37 over the '832 Patent should be withdrawn.

35 USC § 103(a) rejection

Claims 33, 34, 36-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sano T et al. (American Journal of Pathology 153(6): 1741-1748, 1998), in view of O'Brien et al. (U.S. Patent 5,976,799), the MeSH database and Ranki et al.

The cited references, alone or in combination, does not teach or suggest (a) detecting the level of at least one normalization marker characteristic for the presence of endocervical cells; (b) determining the adequacy of the sample based on the levels of the normalization markers detected within the sample solution, and (c) diagnosing cervical dysplasia based on the levels of the relevant markers and the normalization markers.

None of the references, alone or in combination, teach or suggest using a normalization marker characteristic for the presence of endocervical cells in order to characterize the adequacy of the sample, thus avoiding a false negative diagnosis.

Therefore, the 103(a) rejection of Claims 33, 34, 36, and 37 over Sano T et al., in view of O'Brien et al. the MeSH database, and Ranki et al. should be withdrawn.

Double Patenting Rejections

Claims 33, 34, 36-38 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-6 of copending Application No. 10/650,057 in view of the National Library of Medicine's MeSH database and

Ranki et al. Since this is a provisional rejection, Applicants wish to postpone the response to this rejection until the claimed subject matter is otherwise allowable.

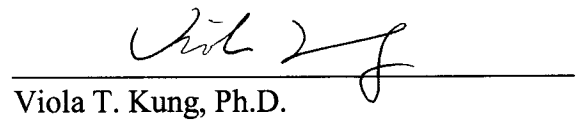
Claims 33, 34, and 36-38 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-5 of U.S. Patent No. 6,709,832 in view of the MeSH database and Ranki et al. As discussed above, the claims of the 832 patent do not recite detecting the level of at least one normalization marker characteristic for the presence of endocervical cells; and determining the adequacy of the sample based on the levels of the normalization markers detected within the sample solution. Therefore, the instant claims are not an obvious variation of those of the '832 Patent. Accordingly, the double patenting rejection of Claims 33, 34, 36 and 37 over the '832 Patent should be withdrawn.

CONCLUSION

Applicants believe that the application is now in good and proper condition for allowance. Early notification of allowance is earnestly solicited.

Respectfully submitted,

Date: January 3, 2007



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